

## CLAIMS

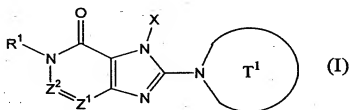
1. A pharmaceutical agent comprising a dipeptidyl peptidase IV inhibitor and a biguanide agent in combination.

2. The pharmaceutical agent according to claim 1, which enhances the effects of active circulating glucagon-like peptide-1 (GLP-1) and/or active circulating glucagon-like peptide-2 (GLP-2).

3. A pharmaceutical agent that enhances the effects of active circulating GLP-2.

4. A pharmaceutical agent comprising a dipeptidyl peptidase IV inhibitor and the pharmaceutical agent according to claim 3 in combination.

5. The pharmaceutical agent according to claim 1 or 4, wherein the dipeptidyl peptidase IV inhibitor is a compound represented by the following formula, or a salt or hydrate thereof,



(wherein,

T¹ represents a monocyclic or bicyclic 4- to 12-membered heterocyclic group containing one or two nitrogen atoms in the ring, that may have one or more substituents;

X represents a C<sub>1-6</sub> alkyl group which may have one or more substituents, a C<sub>2-6</sub> alkenyl group which may have one or more substituents, a C<sub>2-6</sub> alkynyl group which may have one or more substituents, a C<sub>6-10</sub> aryl group which may have one or more substituents, a 5 to 10-membered heteroaryl group which may have one or more substituents, a C<sub>6-10</sub> aryl C<sub>1-6</sub> alkyl group which may have one or more substituents, or a 5 to 10-membered heteroaryl C<sub>1-6</sub> alkyl group which may have one or more substituents;

Z¹ and Z² each independently represent a nitrogen atom or a group represented by the formula -CR²=;

R<sup>1</sup> and R<sup>2</sup> each independently represent a group according to the formula -A<sup>0</sup>-A<sup>1</sup>-A<sup>2</sup>

(wherein A<sup>0</sup> represents a single bond or a C<sub>1-6</sub> alkylene group, which may have 1 to 3 substituents selected from group B consisting of the substituents described below;

A<sup>1</sup> represents a single bond, an oxygen atom, a sulfur atom, a sulfinyl group, a sulfonyl group, a carbonyl group, a group represented by the formula -O-CO-, a group represented by the formula -CO-O-, a group represented by the formula -NR<sup>A</sup>-, a group represented by the formula -CO-NR<sup>A</sup>-, a group represented by the formula -NR<sup>A</sup>-CO-, a group represented by the formula -SO<sub>2</sub>-NR<sup>A</sup>-, or a group represented by the formula -NR<sup>A</sup>-SO<sub>2</sub>-;

A<sup>2</sup> and R<sup>A</sup> each independently represent a hydrogen atom, a halogen atom, a cyano group, a C<sub>1-6</sub> alkyl group, a C<sub>3-8</sub> cycloalkyl group, a C<sub>2-6</sub> alkenyl group, a C<sub>2-6</sub> alkynyl group, C<sub>6-10</sub> aryl group, a 5 to 10-membered heteroaryl group, a 4 to 8-membered heterocyclic group, a 5 to 10-membered heteroaryl C<sub>1-6</sub> alkyl group, a C<sub>6-10</sub> aryl C<sub>1-6</sub> alkyl group, or a C<sub>2-7</sub> alkylcarbonyl group; however, A<sup>2</sup> and R<sup>A</sup> each independently may have 1 to 3 substituents selected from the substituent group B described below:

when Z<sup>2</sup> is a group represented by the formula -CR<sup>2</sup>=, R<sup>1</sup>, and R<sup>2</sup> may in combination form a 5 to 7-membered ring;

except in cases where: [1] R<sup>1</sup> is a hydrogen atom; Z<sup>1</sup> is a nitrogen atom; and Z<sup>2</sup> is -CH=; and [2] Z<sup>1</sup> is a nitrogen atom; and Z<sup>2</sup> is -C(OH)=;

#### <Substituent group B>

Substituent group B represents the group consisting of: a hydroxyl group, a mercapto group, a cyano group, a nitro group, a halogen atom, a trifluoromethyl group, a C<sub>1-6</sub> alkyl group which may have one or more substituents, a C<sub>3-8</sub> cycloalkyl group, a C<sub>2-6</sub> alkenyl group, a C<sub>2-6</sub> alkynyl group, a C<sub>6-10</sub> aryl group, a 5 to 10-membered heteroaryl group, a 4 to 8-membered heterocyclic group, a C<sub>1-6</sub> alkoxy group, a C<sub>1-6</sub> alkylthio group, a group represented by the formula -SO<sub>2</sub>-NR<sup>B1</sup>-R<sup>B2</sup>, a group represented by the formula -NR<sup>B1</sup>-CO-R<sup>B2</sup>, a group represented by the formula -NR<sup>B1</sup>-R<sup>B2</sup> (where R<sup>B1</sup> and R<sup>B2</sup> each independently represent a hydrogen atom or a C<sub>1-6</sub> alkyl group), a group represented by the formula -CO-R<sup>B3</sup> (where R<sup>B3</sup> represents a 4 to 8-membered heterocyclic group), a group represented by the formula -CO-R<sup>B4</sup>-R<sup>B5</sup> and a group represented by the

formula  $-\text{CH}_2-\text{CO}-\text{R}^{\text{B}4}-\text{R}^{\text{B}5}$  (where  $\text{R}^{\text{B}4}$  represents a single bond, an oxygen atom, or a group represented by the formula  $-\text{NR}^{\text{B}6}-$ ;  $\text{R}^{\text{B}5}$  and  $\text{R}^{\text{B}6}$  each independently represent a hydrogen atom, a  $\text{C}_{1-6}$  alkyl group, a  $\text{C}_{3-8}$  cycloalkyl group, a  $\text{C}_{2-6}$  alkenyl group, a  $\text{C}_{2-6}$  alkynyl group, a  $\text{C}_{6-10}$  aryl group, a 5 to 10-membered heteroaryl group, a 4 to 8-membered heterocyclic  $\text{C}_{1-6}$  alkyl group, a  $\text{C}_{6-10}$  aryl  $\text{C}_{1-6}$  alkyl group, or a 5 to 10-membered heteroaryl  $\text{C}_{1-6}$  alkyl group)).

6. The pharmaceutical agent according to claim 5, wherein  $\text{T}^1$  is a piperazin-1-yl group or a 3-amino-piperidin-1-yl group.

7. The pharmaceutical agent according to claim 5, wherein  $\text{T}^1$  is a piperazin-1-yl group.

8. The pharmaceutical agent according to any one of claims 5 to 7, wherein X is a 3-methyl-2-buten-1-yl group, a 2-butenyl group, a benzyl group, or a 2-chlorophenyl group.

9. The pharmaceutical agent according to any one of claims 5 to 7, wherein X is a 2-butenyl group.

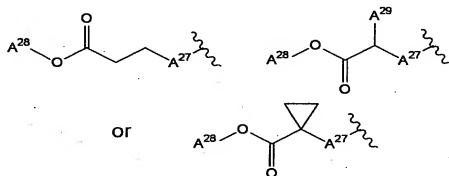
10. The pharmaceutical agent according to any one of claims 5 to 9, wherein,  $\text{Z}^1$  is a nitrogen atom; and  $\text{Z}^2$  is a group represented by the formula  $-\text{CR}_2=$  (where  $\text{R}^2$  is as defined in claim 5).

11. The pharmaceutical agent according to any one of claims 5 to 9, wherein,  $\text{Z}^2$  is a nitrogen atom; and  $\text{Z}^1$  is a group represented by the formula  $-\text{CR}_2=$  (where  $\text{R}^2$  is as defined in claim 5).

12. The pharmaceutical agent according to any one of claims 5 to 11, wherein  $\text{R}^1$  is either a methyl group, a cyanobenzyl group, a fluorocyanobenzyl group, a phenethyl group, a 2-methoxyethyl group, or a 4-methoxycarbonylpipridin-2-yl group.

13. The pharmaceutical agent according to any one of claims 5 to 11, wherein  $\text{R}^1$  is a methyl group, or a 2-cyanobenzyl group.

14. The pharmaceutical agent according to any one of claims 5 to 13, wherein  $R^2$  is either a hydrogen atom, a cyano group, a methoxy group, a carbamoylphenyloxy group, or a group represented by the formula:



(where,

$A^{27}$  represents an oxygen atom, a sulfur atom, or -NH-;

$A^{28}$  and  $A^{29}$  each independently represent a hydrogen atom or a  $C_{1-6}$  alkyl group).

15. The pharmaceutical agent according to any one of claims 5 to 13, wherein  $R^2$  is a hydrogen atom, a cyano group, or a 2-carbamoylphenyloxy group.

16. The pharmaceutical agent according to claim 5, wherein the compound represented by formula (I) is any one compound selected from:

(1) 7-(2-butynyl)-2-cyano-1-methyl-8-(piperazin-1-yl)-1,7-dihydropurin-6-one;

(2)

3-(2-butynyl)-5-methyl-2-(piperazin-1-yl)-3,5-dihydroimidazo[4,5-d]pyridazin-4-one;

(3)

2-(3-aminopiperidin-1-yl)-3-(2-butynyl)-5-methyl-3,5-dihydroimidazo[4,5-d]pyridazin-4-one;

(4) 2-[7-(2-butynyl)-1-methyl-6-oxo-8-(piperazin-1-yl)-6,7-dihydro-1H-purin-2-yloxy] benzamide;

(5)

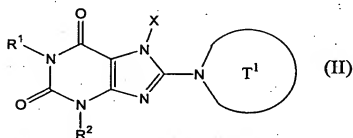
7-(2-butynyl)-1-(2-cyanobenzyl)-6-oxo-8-(piperazin-1-yl)-6,7-dihydro-1H-purine-2-carbonitrile; and

(6) 2-[3-(2-butynyl)-4-oxo-2-(piperazin-1-yl)-3,4-dihydroimidazo[4,5-d]pyridazin-5-ylmethyl] benzonitrile;

or a salt or hydrate thereof.

17. The pharmaceutical agent according to claim 1 or 4, wherein the dipeptidyl

peptidase IV inhibitor is a compound represented by the following formula, or a salt or hydrate thereof,



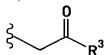
(wherein  $T^1$ ,  $X$ ,  $R^1$ , and  $R^2$  are as defined in claim 5).

18. The pharmaceutical agent according to claim 17, wherein  $T^1$  is a piperazin-1-yl group.

19. The pharmaceutical agent according to claim 17 or 18, wherein  $X$  is a 2-butyryl group or a 2-chlorophenyl group.

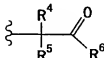
20. The pharmaceutical agent according to claim 17 or 18, wherein  $X$  is a 2-butyryl group.

21. The pharmaceutical agent according to any one of claims 17 to 20, wherein  $R^1$  is a hydrogen atom, a methyl group, a 2-propynyl group, a 2-butyryl group, a cyanomethyl group, a phenethyl group, a phenoxyethyl group, or a group represented by the formula:



(where  $R^3$  represents a hydroxyl group, a  $C_{1-6}$  alkoxy group, or a phenyl group).

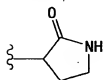
22. The pharmaceutical agent according to any one of claims 17 to 21, wherein  $R^2$  is a hydrogen atom, a  $C_{1-6}$  alkyl group, an ethoxyethyl group, a tetrahydrofuranylmethyl group, or a group represented by the formula:



(where,

$R^4$  and  $R^5$  are identical to or different from each other, and independently represent a hydrogen atom, a methyl group, or a phenyl group; and

R<sup>6</sup> represents a hydroxyl group, a C<sub>1-6</sub> alkoxy group, or a phenyl group),  
or a group represented by the formula:



23. The pharmaceutical agent according to claim 17, wherein the compound represented by formula (II) is any one compound selected from:

(1) 7-(2-butynyl)-1,3-dimethyl-8-(piperazin-1-yl)-3,7-dihydropurine-2,6-dione;

(2) 7-(2-butynyl)-3-methyl-8-(piperazin-1-yl)-3,7-dihydropurine-2,6-dione;

(3) methyl

[7-(2-butynyl)-3-methyl-2,6-dioxo-8-(piperazin-1-yl)-2,3,6,7-tetrahydropurin-1-yl] acetate;

(4)

7-(2-butynyl)-3-methyl-8-(piperazin-1-yl)-1-(2-propynyl)-3,7-dihydropurine-2,6-dione;

(5) 1,7-bis(2-butynyl)-3-methyl-8-(piperazin-1-yl)-3,7-dihydropurine-2,6-dione;

(6) [7-(2-butynyl)-3-methyl-2,6-dioxo-8-(piperazin-1-yl)-2,3,6,7-tetrahydropurin-1-yl] acetonitrile;

(7)

7-(2-butynyl)-3-methyl-1-[(2-oxo-2-phenyl)ethyl]-8-(piperazin-1-yl)-3,7-dihydropurine-2,6-dione;

(8) 7-(2-butynyl)-3-ethyl-1-methyl-8-(piperazin-1-yl)-3,7-dihydropurine-2,6-dione;

(9) methyl

[7-(2-butynyl)-1-methyl-2,6-dioxo-8-(piperazin-1-yl)-1,2,6,7-tetrahydropurin-3-yl] acetate;

(10)

7-(2-butynyl)-3-(2-tetrahydrofuranyl)methyl-1-methyl-8-(piperazin-1-yl)-3,7-dihydropurine-2,6-dione;

(11) methyl

[7-(2-butynyl)-1-methyl-2,6-dioxo-8-(piperazin-1-yl)-1,2,6,7-tetrahydropurin-3-yl]phenylacetate;

(12) 7-(2-butynyl)-3-propyl-1-methyl-8-(piperazin-1-yl)-3,7-dihydropurine-2,6-dione;

(13)

7-(2-butynyl)-3-(2-oxo-2-phenethyl)-1-methyl-8-(piperazin-1-yl)-3,7-dihydropurine-2,6-dione;

- (14) ethyl  
2-[7-(2-butynyl)-1-methyl-2,6-dioxo-8-(piperazin-1-yl)-1,2,6,7-tetrahydropurin-3-yl]  
propionate;
- 5 (15)  
7-(2-butynyl)-3-(2-ethoxyethyl)-1-methyl-8-(piperazin-1-yl)-3,7-dihydropurine-2,6-dione;
- (16)  
7-(2-butynyl)-3-isopropyl-1-methyl-8-(piperazin-1-yl)-3,7-dihydropurine-2,6-dione;
- 10 (17)  
7-(2-butynyl)-3-(3,3-dimethyl-2-oxobutyl)-1-methyl-8-(piperazin-1-yl)-3,7-dihydropurine-2,6-dione;
- (18)  
7-(2-butynyl)-1-methyl-3-(2-oxopyrrolidin-3-yl)-8-(piperazin-1-yl)-3,7-dihydropurine-2,6-dione;
- 15 (19)  
7-(2-butynyl)-3-(2-ethoxyethyl)-1-(2-oxo-2-phenylethyl)-8-(piperazin-1-yl)-3,7-dihydropurine-2,6-dione;
- (20) methyl  
[7-(2-butynyl)-2,6-dioxo-1-(2-oxo-2-phenylethyl)-8-(piperazin-1-yl)-1,2,6,7-tetrahydropurin-3-yl] acetate;
- 20 (21) ethyl  
[7-(2-butynyl)-2,6-dioxo-1-(2-phenethyl)-8-(piperazin-1-yl)-1,2,6,7-tetrahydropurin-3-yl] acetate;
- (22)  
25 [7-(2-butynyl)-2,6-dioxo-1-(2-phenethyl)-8-(piperazin-1-yl)-1,2,6,7-tetrahydropurin-3-yl] acetate;
- (23)  
7-(2-butynyl)-3-[2-oxo-2-(pyrrolidin-1-yl)ethyl]-1-(2-phenethyl)-8-(piperazin-1-yl)-3,7-dihydropurine-2,6-dione;
- 30 (24)  
2-[7-(2-butynyl)-2,6-dioxo-1-(2-phenethyl)-8-(piperazin-1-yl)-1,2,6,7-tetrahydropurin-3-yl]-N-methylacetamide;
- (25)  
2-[7-(2-butynyl)-2,6-dioxo-1-(2-phenethyl)-8-(piperazin-1-yl)-1,2,6,7-tetrahydropurin-3-yl]-N-cyclopropyl acetamide;
- 35 (26)

2-[7-(2-butynyl)-2,6-dioxo-1-(2-phenethyl)-8-(piperazin-1-yl)-1,2,6,7-tetrahydropurin-3-yl]-N-phenylacetamide; and  
(27)

2-[7-(2-butynyl)-2,6-dioxo-1-(2-phenethyl)-8-(piperazin-1-yl)-1,2,6,7-tetrahydropurin-3-yl]-N-(2-propynyl) acetamide;

or a salt or hydrate thereof.

24. The pharmaceutical agent according to claim 1, wherein the biguanide agent is metformin.

25. The pharmaceutical agent according to claim 1 or 2, which is a preventive or therapeutic agent for a disease which is associated with active circulating GLP-1 and/or active circulating GLP-2.

26. The pharmaceutical agent according to claim 25, wherein the disease is at least any one selected from the group consisting of: diabetes, obesity, hyperlipidemia, and gastrointestinal diseases.

27. The pharmaceutical agent according to claim 3 or 4, which is a preventive or therapeutic agent for a disease which is associated with active circulating GLP-2.

28. The pharmaceutical agent according to claim 27, wherein the disease is a gastrointestinal disease.

29. A method for preventing or treating a disease which is associated with active circulating GLP-1 and/or active circulating GLP-2, which comprises administering the pharmaceutical agent according to claim 1 or 2 at an effective amount.

30. The use of the pharmaceutical agent according to claim 1 or 2 for producing a preventive or therapeutic agent for a disease which is associated with active circulating GLP-1 and/or active circulating GLP-2.

31. A method for preventing or treating a disease which is associated with active circulating GLP-2, which comprises administering the pharmaceutical agent according to claim 3 or 4 at an effective amount.



32. The use of the pharmaceutical agent according to claim 3 or 4 for producing a preventive or therapeutic agent for a disease which is associated with active circulating GLP-2.

33. A method for enhancing the effects of active circulating GLP-1 and/or active  
5 circulating GLP-2, which comprises using the pharmaceutical agent according to claim 1 or 2.

34. A method for enhancing the effects of active circulating GLP-2, which comprises using the pharmaceutical agent according to claim 3 or 4.